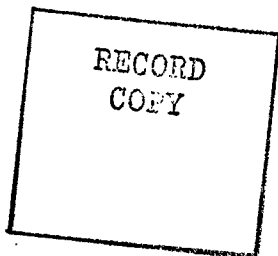


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REVIEW OF THE CONFERENCE ON PROBLEMS IN PHYSIOLOGICAL REGENERATION

- USSR -

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REVIEW OF THE CONFERENCE ON PROBLEMS IN PHYSIOLOGICAL REGENERATION

Following is an article by L. D. Liozner and V. N. Dobrokhotoy in Uspekhi Sovremennoy Biologii (Advances in Modern Biology), Vol. XLVIII, No. 2(5), Moscow 1959, pages 239-244.

A conference on problems in physiological regeneration -- called at the suggestion of the Problem Committee on Regeneration -- was held from 11 to 14 May in Sukhumi at the Institute of Experimental Pathology and Therapy, Academy of Medical Sciences USSR, which helped to organize the conference. Some 150 persons from various scientific institutions in Moscow, Leningrad, Sukhumi, Tiflis, Frunze, Kursk, Ryazan', and Stalino attended and heard over 40 reports.

The reason for the conference -- first of its kind ever held -- is the recent advances in the field of physiological regeneration. Soviet histologists and biologists typically regard tissues as dynamic structures constantly undergoing renewal, i.e., physiological regeneration. The exceptional importance of investigating physiological regeneration to solve biological and medical problems was demonstrated in recent years by G. K. Khrushchov, A. N. Studitskiy, M. A. Vorontsova, L. D. Liozner, and others. There has been increased interest in the subject abroad. The conference treated problems in physiological regeneration in close association with cell multiplication.

In his introductory remarks V. Kh. Vasilenko, a member of the Presidium of the Academy of Medical Sciences USSR, discussed the great significance of regeneration for medicine, stressing the need of acquainting physicians with the present state of the problem.

The first report, "Main Tasks in the Study of Physiological Regeneration," was presented by L. D. Liozner, who developed the idea that physiological regeneration exists at various levels: organic, tissue, and intracellular. Viewed in this fashion, physiological regeneration is both a result of the functioning of organs and a necessary condition for normal activity. The speaker emphasized the importance of employing new methods of investigation because the processes of tissue restoration are frequently difficult to trace. He pointed out that we still know too little about the connection between physiological regeneration and metabolism, post-traumatic regeneration and various pathological disorders (malignant growth, etc.).

In his report on "Principles Underlying the Histogenesis and Regeneration of Tissues," S. I. Shchelkunov concentrated on the relationship between mitosis and amitosis during growth and differentiation. He reached the general conclusion that cambial cellular elements divide largely by mitosis

whereas differentiated cells divide by amitosis. A shift from one of these methods of multiplication to the other is possible.

S. Ya. Zalkind, V. G. Zaslavskiy, T. G. Orlova, and N. B. [later given as N. V.] Borisoglebskaya spoke on "Some Principles Underlying the Multiplication of Cells Cultivated Outside of the Organism," describing methods of multiplication used by cells of different strains, including strains of malignant tumors.

During the ensuing discussion A. N. Studitskiy criticized the view that renewal of some tissues is possible only on the intracellular or molecular level on the grounds that it implies the presence of stable organs in which the cellular element is not renewable.

L. D. Liozner pointed out that general discussions of amitosis are scarcely justified and that precise qualitative methods must be devised.

A. A. Braun raised a question as to the significance of the form of renewal that takes place when only part of the cell (apocrine secretion) dies. He cited instances where differentiation between the tissue and intracellular levels of renewal was difficult.

L. N. Zhinkin stressed the value of studying physiological regeneration in conjunction with metabolism. He noted that the methods of regeneration were varied and included renewal both of the cell as a whole and of its constituent parts.

V. P. Mikhaylov said that there should not be any preconceived notions of physiological regeneration, that the process had to be minutely examined.

A. S. Lezhava, G. S. Strelin, and S. Ya. Zalkind took part in the discussion.

The next report, "Use of Tritium in the Composition of Thymidine in Cytoradiographic Research," was by G. S. Strelin. The author pointed out the advantages of using thymidine in obtaining autoradiograms. He also observed that it is contained only in the DNA of chromosomes at a certain stage in cell development.

In his paper "Chemical Differentiation in the Physiological Regeneration of Certain Cambial Tissues," L. N. Zhinkin cited data that he and his co-workers obtained with the help of radioactive isotopes. They found selective inclusion of different substances in individual tissues, concluding that the most intensive exchange takes place in poorly differentiated cells.

Discussing "The Influence of External and Internal Environmental Factors on Physiological Regeneration of the Epidermis," A. A. Braun presented a wealth of data to show that such factors as ultraviolet radiation and X-rays, the application of ceresin, paraffin, etc., which cause hypertrophy or atrophy of the skin, impair physiological regeneration and lead to the predominance of destructive or reparative processes.

In his paper "Thorny Problems Connected with Physiological Regeneration of Small Intestine Epithelium," N. P. Bochkov insisted that the separation of epithelium from the villi in the form of solid tubules observed by M. I. Rasumov is an artefact caused by fixation.

During the discussion A. N. Studitskiy, L. D. Liozner, V. P. Mikhaylov, and I. A. Utkin said that the data of L. N. Zhinkin and N. P. Bochkov were of interest, but they directed attention to the difficulty of studying destructive processes in physiological regeneration. That is why it is particularly important to use radioactive isotopes, specifically labeled tritium.

The second session heard a group of reports on the daily periodicity of mitotic division.

In his paper "The Present Status of the Problem of the Daily Rhythm of Mitotic Cell Division in Animals," V. N. Dobrokhotoy described the main directions and tasks of research in the field, stressing the need for standardizing the conditions of experimentation in order to obtain comparable data.

L. D. Liozner and V. F. Sidorova in their paper "Physiological Regeneration in the Liver" demonstrated the existence of a daily rhythm of mitosis in the liver of adult mice. The authors discovered the largest number of mitoses in the early morning hours, the smallest number during the day.

V. V. Kozlov's report, "Mechanism of Daily Cycles of Mitotic Activity," contained data showing that removal of the rat suprarenals disturbs the daily cycle of mitotic activity in several tissues.

L. P. Kosichenko discussed "Daily and Seasonal Periodicity of Mitosis in the Corneal Epithelium of Laboratory Animals," showing that the daily periodicity of mitosis in rats and mice is independent of the season.

A. N. Studitskiy said that the reports were of great value, particularly the findings of L. D. Liozner and V. F. Sidorova. He emphasized, however, that one must not consider mitosis the only method by which physiological regeneration of tissues can be achieved. Amitosis and other ways of forming new cells have been little studied.

L. D. Liozner said that the data on daily rhythm of mitosis are highly contradictory. He urged that at least the main conditions of experimentation should be standardized so as to ensure the obtaining of unambiguous results.

V. N. Dobrokhotoy in commenting on V. V. Kozlov's paper expressed his desire to investigate in the same way other tissues, particularly intestinal epithelium.

G. S. Strelin presented data obtained by his laboratory confirming the results of L. D. Liozner and V. F. Sidorova's experiments.

L. N. Zhinkin noted that the general level of mitotic activity remains substantially unchanged despite regular shifts in the number of mitoses during the day.

S. I. Shchelkunov emphasized that mitotic activity should not be studied without reference to morphological changes in the tissues.

M. T. Gololobova maintained that L. P. Kosichenko's data on seasonal changes in mitotic activity require confirmation by experiments reflecting the natural conditions in which the animals are kept.

Commenting on the data of L. D. Liozner and V. F. Sidorova, N. I. Grigor'yev pointed out that he was able to find a very small number of mitoses in his examination of many sections of animal liver during the day.

V. M. Mastryukova expressed the view that the main task in investigating mitotic activity today is to search for the underlying regulatory mechanisms.

V. P. Mikhaylov stressed the fact that science still has no evidence of a single instance of new cells forming other than by mitosis or amitosis.

I. A. Utkin noted the difficulty in counting amitotic figures due to the lack of clear criteria therefore and of information on the duration of amitosis.

In contrast with S. I. Shchelkunov's view, S. Ya. Zalkind said that investigations of mitotic activity are increasingly accompanied by profound morphological analysis. The renewal processes are not limited to mitotic division of cells. However, the inadequacy of data on the role of amitosis does not diminish the importance of materials obtained in studying mitosis.

The same session heard reports on the influence of sex hormones on mitotic activity of tissues.

O. I. Yepifanova in her paper, "The Effect of Folliculin and Progesterone on the Mitotic Activity of the Epithelium of the Mouse Endometrium," showed that changes in the number of mitoses observed after the administration of hormones are due to morphological reconstruction in the uterus and that they depend on the original condition of the tissue.

S. S. Laguchev reported on "The Effect of Ovarian Hormones on the Mitotic Activity of Mammary Gland Epithelium." He described the dynamics of changes in the number of mitoses in the epithelium of the gland after injecting mice with sex hormones and traced the processes of proliferation and destruction in this organ.

V. P. Mikhaylov stressed the value of the data presented in these reports, but urged that these problems be studied in conjunction with various pathological processes. He said that the materials submitted should be discussed with pathologists.

At the third session I. A. Utkin, M. V. Avdzhian, and Yu. P. Butnev showed in their paper, "An Investigation of Cell Divisions in Corneal Epithelium Incubated Outside the Organism," that under these conditions the entrance of corneal epithelial cells into mitosis is disturbed, although the duration of mitosis remains unchanged. Certain mitotic poisons which impair respiration, oxidative phosphorylation, and glycolysis markedly affect the rate of mitosis.

In his "Duration of Mitosis and Rate of Physiological Regeneration in Rat Intestinal Epithelium," N. P. Bochkov showed that the duration of mitosis in this tissue is much shorter than hitherto assumed. He studied changes in mitotic phases after irradiating the animals with X-rays and γ -rays.

Reporting on "Mitosis and Amitosis in Giant Cells of the Trophoblast and in Decidual Cells," Ye. V. Zyбина described the pattern of change from mitotic to amitotic multiplication of cells during development of the decidua.

She traced in detail the processes involved in transforming trophoblast cells into giant cells containing polyploid nuclei produced by endoamitosis.

O. T. Movchan read a paper on "Mitotic Activity of the Corneal Epithelium of Completely Fasted White Rats and White Mice." The speaker pointed out the relationship between animal body weight and change in mitotic activity during prolonged starvation.

G. S. Uspenskaya and A. B. Kalneniek presented a communication entitled "Mitotic Activity of Epithelium in the Mucosa of the Oral Cavity and Intestine in Some Mammals." They showed that fasted guinea pigs and rabbits exhibit a decreased number of mitoses in the epithelium of the mucosa of the oral cavity right after feeding. This later gives way to a substantial rise in mitotic activity.

L. N. Moralov reported on "Destructive and Regenerative Phenomena in the Pancreas After Local Disorders of Blood Circulation." Using his own method of applying movable wire ligatures to blood vessels, he was able to effect in cats temporary impairment of circulation in the region of the gland. At the same time he observed variations in the reconstruction of this organ, the degree depending on the length of time the flow of blood was blocked.

During the course of the discussion N. I. Grigor'yev noted that rapid changes in intestinal epithelium cannot be observed in reparative regeneration of the mucosa of the intestine.

S. I. Shchelkunov said that the reports presented at the preceding sessions were indicative of the considerable progress made in studying the patterns of cell multiplication in the organism. It would be desirable, he added, if all research included an investigation of structural changes in tissues.

V. M. Dobrokhotov stated that the data obtained by I. A. Utkin in tissue transplantation were of great value. The long periods of animal starvation in G. S. Uspenskaya and A. B. Kalneniek's investigation were not justified.

V. Kh. Vasilenko said that the reports and discussions of the past two days clearly showed that a large amount of interesting material is now available on physiological regeneration and that it needs to be circulated more widely. Not enough has been done to bring it to the attention of clinicians, who often require information on the rate and forms of self-regeneration of different tissues under normal and pathological conditions. Accordingly, there should be more summaries published on various aspects of the problem along with wider use of medical journals.

At the fourth session S. Ya. Zalkind and N. V. [sic?] Borisoglebskaya read a paper on "Mitotic Activity of the Organism in the Process of Elaborating Immunity to Poliomyelitis." The authors showed that injecting rats with active poliomyelitis vaccine stimulates mitotic activity in the spleen and cornea.

Ya. Ye. Khesin, O. F. Sarycheva, T. V. Voronina, E. P. Pille, Yu. N. Mastyukova, and K. S. Blinnikova presented a report on "A Karyometric Investigation of Single-Layer Tissue Cultures Under Normal Conditions and After the Action of Certain Viruses." The authors showed that certain viruses cause the average size of nuclei to increase and bring about morphological changes in the cells of cultures due to destruction of the physico-chemical properties of nuclear colloids.

Ye. S. Tsareva's paper, "The Influence of Vegetotropic Substances on Mitosis in Corneal Epithelium," showed that heightened tonus of the parasympathetic nervous system stimulates mitosis, whereas heightened tonus of the sympathetic system inhibits it.

L. I. Omel'yanenko in her report on "Mitosis in the Epithelium of Crypts in the Rat Small Intestine With Impaired Innervation" cited data showing that the number of mitoses decreases following ligation of the neurovascular tract leading to certain portions of the intestine.

During the ensuing discussion I. A. Utkin emphasized that the data presented in some reports on changes in mitotic phases as an indicator of changes in mitotic activity must be very cautiously interpreted.

A. N. Studitskiy mentioned the need of having an accurate idea of the nature of the influence exerted by the nervous system on the regulation of mitosis in tissues. He asked whether the nervous system acts directly on mitosis or whether its action is mediated by metabolic processes. This question provoked a lively exchange of views. Most of the speakers (V. P. Mikhaylov, V. N. Dobrokhotoy, and G. S. Strelin) asserted that this influence should be regarded as mediated, but its nature has scarcely been studied. S. Ya. Zalkind agreed, advancing the hypothesis that in some cases the nervous system might act in more direct fashion on cell division. L. D. Liozner held that the question required a deeper theoretical analysis.

V. N. Dobrokhotoy discussed some errors in method made by L. I. Omel'yanenko in connection with counting mitoses in the intestine. He noted the value of Ye. S. Tsareva's data.

Commenting on the materials presented in Ya. Ye. Khesin and co-workers' report, L. N. Zhinkin said that he wished tseytrafernyaya s'yemka were employed. He stressed the undesirability of using one portion of the intestine as a control for another, as was done by L. I. Omel'yanenko.

S. Ya. Zalkind in commenting on Ya. Ye. Khesin's report said that it would be desirable to study changes in the size of the nuclei and nature of the morphological aberrations in cultures as they age.

G. S. Strelin pointed out some contradictions between the data of Ye. S. Tsareva and those of workers in his laboratory.

S. I. Shchelkunov held that the results of Ye. S. Tsareva's experiments might be explained as caused by vascular reaction to the injected substances. L. I. Omel'yanenko's experiments were not wholly convincing because the corresponding portions of the intestine were not denervated.

The same session heard the paper of N. I. Grigor'yev, "Correlation Between Physiological and Reparative Regeneration of Epithelia of the Intestinal Type." Basing his observations on various groups of vertebrates,

the author advanced the view that the rate of regeneration of various entodermal derivatives after suffering injury is directly related to their inherent level of physiological regeneration.

Reporting on "Reparative Regeneration of Normal and Pathologically Changed Liver in Mammals," B. P. Solopayev cited the results of a morphological and physiological investigation of reparative regeneration in monkey liver and the capacity for regeneration of cirrhotic rabbit liver. In addition, he demonstrated the relationship between rate of liver regeneration and changes in the functional state of the liver.

L. M. Mirtova discussed "Regeneration of the Peripheral Nerve in Monkeys and Other Types of Animals in Ontogenesis." She showed that transected sciatic nerve regenerates more quickly in young monkeys and rabbits than in older animals.

In his "Changes in Nucleic Acids During Physiological and Reparative Regeneration of Epithelium in the Mucous Membrane of the Tongue of White Mice," Yun' Li-yun' presented data on changes in the quantity and distribution of nucleic acids in the nuclei and cytoplasm of the epithelium after injury.

During the discussion A. N. Studitskiy stressed the presence of a direct relationship between the capacity for physiological and reparative regeneration and the level of metabolism. In this connection he examined the results obtained by B. P. Solopayev on characteristics of the processes of liver regeneration in monkeys and other mammals and L. M. Mirtova's data on nerve regeneration in animals of different age groups.

Commenting on N. I. Grigor'yev's paper, L. D. Liozner noted that injury of the intestinal wall results not only in tissue but also in organ regeneration.

S. I. Shchelkunov pointed out the value of the morphophysiological approach to reparative regeneration in B. P. Solopayev's research, adding that histochemical investigations should also be conducted in this field.

The first speaker in the fifth session was M. F. Merkulov, who discussed "The Inclusion of Labeled Amino Acids in Proteins as an Indicator of the Rate of Renewal." He maintained that cell division and increase in the mass of tissues proceed against a background of more rapid restoration of their molecular structure, which should be taken into account when analyzing the data of autoradiography in connection with physiological regeneration.

The paper of A. A. Manina and L. I. Chekulayeva, "Autoradiographic Investigation of the Effect of Temperature on Protein Exchange and Physiological Regeneration," demonstrated the existence of differences in the reaction of brain and epidermal tissues to temperature. This factor was the cause of marked retardation or acceleration of the process of cell change in the epidermis, whereas in the brain there were only swift and transient changes.

In his report "Morphophysiological Evidence Relating to the Ability of the Frog Myocardium to Regenerate Completely," P. P. Romyantsev cited data indicating the presence of regenerative processes after he squeezed

the frog stomach with pincers following removal of the apex of the stomach from the remaining portion of the area of necrotic tissue.

I. A. Poberiy reported on "A Microautoradiographic Investigation of Regenerative Processes in Hematopoietic Organs," discussing the different rates of inclusion of labeled sulfur in elements of bone marrow and the eventual fate of the labeled cells.

In her paper "Regenerative Processes in Bone Marrow after Inducing Anemia in Animals and Injecting Blood Substitutes," S. A. Tsygankova described stimulation of the regenerative processes in bone marrow under the influence of hydrolyzates.

This session also heard the report of A. M. Chernukh and P. N. Alexandrov on "The Effect of Antibiotics on Tissue Regeneration in the Inflammatory Focus and on Development of the Chick Embryo" and the report of Lyu-Tszyan'-chan on "Regenerative Phenomena in Tissues of the Uterine Wall of White Rats following the Injection of a Foreign Body."

During the discussion O. T. Movchan and A. A. Braun noted the value of the data on physiological regeneration obtained by autoradiography and commented on the pertinent reports.

V. P. Mikhaylov said that P. P. Rumyantsev's data convincingly demonstrated the capacity of the frog myocardium for regeneration. He pointed out that the last two reports dealt with inflammation rather than regeneration.

A. N. Studitskiy expressed the view that the existence of special biochemical regeneration independent of tissue regeneration was highly doubtful. Cell regeneration is characteristic of all tissues.

L. N. Zhinkin thought that the reports of M. F. Merkulov and I. A. Poberiy were interesting, but did not have enough morphological data. Differing with A. N. Studitskiy, L. N. Zhinkin maintained that there are tissues, e.g., in the nervous system, where cell renewal is weakly pronounced, but protein exchange may be intensive.

S. Ya. Zalkind expressed the wish that mitotic activity of tissues be studied in experiments concerned with the effect of antibiotics on inflammation and embryonic development.

The sixth session was devoted solely to the effect of penetrating radiation on physiological and reparative regeneration.

In his paper on "Basic Directions in the Study of Tissue Reparative Processes After Radiation Injury," V. P. Mikhaylov noted three directions: repair of tissue injury caused by brief exposure, post-traumatic regeneration following radiation, and physiological regeneration in the presence of small, prolonged irradiation doses. The author stressed the fact that it would be incorrect to regard the inhibition of regenerative capacity after radiation as the general rule, for it often develops as a result of side effects of irradiation (infection, necrosis of tissues, etc.).

G. S. Strelin reported on "New Data Concerning the Restoration of Hematopoiesis in Irradiated Animals by Transplantation of Bone Marrow Cells." He discussed the results of foreign research dealing with ways of preventing the death of animals that have received lethal doses of rays by auto- and homoplastic transplantation of bone marrow cells.

Ye. V. Dmitriyeva discussed "Post-traumatic Regeneration of the Skeletal Musculature Under Different Conditions of Irradiation With Roentgen Rays." T. L. Sopova and N. V. Smirnov gave a paper on "Bone Regeneration After Traumatic Injury in Acute Radiation Sickness." The authors demonstrated the presence of restorative processes in the muscles and bones even after substantial irradiation doses.

V. Ya. Karmysheva reported on "Reactive and Regenerative Processes in Ovaries After Ionizing Irradiation." The speaker described the restorative as well as destructive processes in irradiated ovaries.

N. F. Barakina delivered a paper entitled "An Investigation of the Processes of Destruction and Regeneration in the Hematopoietic System After Radiation" in which she cited data relevant to the prevention of the death of irradiated rats injected with a suspension of bone marrow cells.

The last report, "Changes in the Mitotic Activity of Cells and Chromosome Injury as Factors Limiting Tissue Regeneration After Radiation," was presented by I. M. Shapiro. He showed that repeated hepatectomy causes the swift disappearance of cells with chromosome aberrations in irradiated animals. He traced changes that take place in the tissues of animals irradiated in an atmosphere of carbon monoxide.

L. N. Zhinkin and G. S. Strelin said during the discussion that they did not agree with the division of different methods of tissue repair suggested by V. P. Mikhaylov. G. S. Strelin pointed out that he had never maintained that inhibition of regeneration by irradiation was a general rule.

A. A. Braun stated that Ye. V. Dmitriyeva's data did not agree with those of other authors who had demonstrated the inhibition of muscle regeneration after irradiation.

V. F. Sidorova, N. S. Artem'yeva, S. Ya. Zalkind, I. A. Utkin, and L. D. Liozner also commented on various reports.

The participants in the conference passed a resolution noting the substantial progress made by the Soviet Union in the field of physiological regeneration. Nevertheless, they held, it is necessary to expand research and utilize the latest techniques, particularly radioactive isotopes. In addition, the importance of bringing the resultant data and findings to the attention of investigators in various fields and physicians was underlined.